

## REMARKS

Claims 1-9, 11-21, 23-29, 31-41 are pending. Claims 38 and 40 are herewith amended. Claims 42 and 43 are new and are described in the specification, *inter alia*, at page 7, last paragraph to page 8, first paragraph. Now new matter is added with these new claims or any of the amendments.

### I. CLAIM OBJECTION

In paragraph 6, the Examiner has objected to claim 38 for the asserted reason that the term "polylysine" should be "poly-lysine." In response, applicants have amended claim 38 to recite "poly-lysine"; withdrawal of this objection is therefore respectfully requested.

### II. PRIORITY

The Examiner maintains that claims 1 and 18, reciting a method of reducing kidney retention of a protein conjugate, are not entitled to the benefit of the filing date of USSN 08/407,899, March 21, 1995, for the asserted reason that the species "antibodies" disclosed in USSN 08/407,899 does not support the genus "protein conjugate," of claims 1 and 18. The Examiner also alleges that the glycoprotein conjugates and of lipoprotein conjugates of claim 2 do not find support in USSN 08/407,899. Applicants respectfully but vigorously traverse this conclusion.

The basic rule is that in order for a claim in a continuation-in-part application ("CIP") to be entitled to the filing date of an earlier application, the earlier application must comply with the requirements of 35 USC § 112, first paragraph. That is, the earlier application must provide a written description of the later claimed invention, enable the skilled artisan to make and use the invention and provide the best mode known to the inventor, at the time of filing, for practicing the invention. In order to meet the written description requirement, the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was **in possession of the invention**. *Vas-Cath Inc. v. Mahurkar* 935 F.2d 1555, 19 USPQ 2d 1111 (Fed. Cir. 1991) (emphasis added). Thus, the adequacy of the description is judged from the viewpoint of one of ordinary skill in the art of the invention and involves questions of fact.

A classic text book example illustrating a CIP's entitlement to a parent application's filing date involves the case of the green widgets.<sup>1</sup> The first patent application describes green widgets; the later CIP describes green and yellow widgets and claims generic widgets, green widgets and yellow widgets. More than one year prior to filing the second application, the applicant sells green widgets. The question is whether the claims in the CIP are anticipated by the sale of the green widgets. According to the text book, the claims directed to the generic widgets and the green widgets are entitled to the benefit of the filing date of the parent case because the parent application fully supports such claims. The above example is simple, straightforward and easy to understand: the single species in the parent case is adequate support for the later claimed genus that encompasses the species. This example is, however, just a hypothetical, albeit an often repeated hypothetical used to train patent practitioners. The case law is not so clear and predictable with regard to what is or is not an adequate written description; the facts of each case vary as do the context in which written description issues arise (*e.g.* interferences, amendments and new matter, U.S. continuation and foreign priority questions). However, if the logic of the above hypothetical were applied to the present facts, the generic claims to protein conjugates in the present application would be entitled to the benefit of the March 21, 1995 filing date of the parent application. Applicants assert that such logic should be applied and that the facts of this case would support the same outcome as in the hypothetical.

The parent application, 08/407,899, now U.S. Patent No. 5,843,894 ("the '894 patent"), discloses a solution to the problem involving the renal uptake of molecules that are smaller than 60 kD. (Column 1, lines 33-36). This is a particular problem in immunotherapy and immunodiagnostics where such molecules are labeled with radioisotopes. The '894 patent describes how molecules smaller than 60 kD are filtered by the glomeruli and subsequently reabsorbed in the renal tubule for subsequent lysosomal degradation. When such molecules are radiolabeled, the radiometals stay in the kidney binding to intracellular proteins with high affinity for metal ions. (Column 1, lines 33-38) The retention of radiometals in the kidney leads to nephritic syndrome and renal insufficiency. The '894 patent describes how others have

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<sup>1</sup> Gardner, P.L. and Kayton, I., *Patent Resources Institute, Inc.* Vol. 2, Sect. 6.25 Eighth Ed. (2004)

recognized this problem and offered other solutions, namely treatment with basic L-amino acids to reduce the uptake of radiolabeled peptides and antibody fragments.(Column 1, lines 39-50.)

Although the above discussion is mostly in the "Background of the Invention" part of the specification, this discussion is highly relevant to the claimed invention because it defines the problem addressed by the claimed invention. More specifically, it defines the universe of proteins that creates the problem solved by the invention. What the proteins in that universe have in common is a certain size which causes them to be retained in the kidney. Although the precise mechanism by which antibody fragments find their way into and are retained by the kidney is not explained in the specification, it is clear that antibody fragments conjugated to radiometals and cytotoxic agents do find their way into the kidney where the consequent retention of radiometals and cytotoxic agents can cause renal nephrotoxicity. The invention provides methods to reduce or eliminate this problem. The method by which this problem is solved in the '894 patent is the same method claimed in the present application, *i.e.* the administration to a patient of one or more compounds selected from the group consisting of D-lysine, poly-lysine having a molecular weight in the range 1-60 kD, pharmaceutically acceptable salts thereof and carboxyl derivatives thereof.

Previously presented claim 1 and currently amended claim 38 recite a protein conjugate having a specific molecular weight: **not greater than about 60 kD**. This is the same size molecule described in the '894 patent as being filterable by the glomeruli and thereby retained in the kidney. Thus, claims 1 and 38 recite the type of protein conjugate addressed by the invention claimed in the '894 patent. Present claim 18 also recites a size limitation of the protein conjugate and further describes the conjugate as being a "targeting protein conjugate." It is clear that the '894 patent describes targeting protein conjugates, *i.e.* antibody fragments conjugated with radioisotopes or cytotoxic agents. Applicants draw the Examiner's attention to these claim recitations to emphasize their connection to the basic invention disclosed in the '894 patent. With reference to the above hypothetical, the "widget" of the present invention and the invention described and claimed in the '894 patent is a protein conjugate that is capable of being retained by the kidney. Such proteins are of a size that permits filtration by the glomeruli. In the '894 patent, such proteins are antibody fragments; in the present application such proteins could be antibody fragments or any other protein conjugate of a specific size that is retained in the kidney.

In view of the above explanation, applicants respectfully request the Examiner to reconsider and grant the claims in the present application the benefit of the filing date of the '894 patent.

### **III. PREVIOUS REJECTIONS**

Applicants acknowledge with appreciation the Examiner's withdrawal of the previous rejection of claims 1-21 and 23-37 as being obvious over Behr *et al*, *Cancer Research* 55: 3825-3834 (Sept. 1, 1995) and in view of Grey *et al.*, U.S. Patent No. 5,380,513 and Raines, U.S. Patent No 5,840,296.

### **IV. NEW GROUNDS OF REJECTION**

#### **A. Rejection under 35 USC § 112**

In paragraph 10, the Examiner rejects claim 38 under 35 USC § 112, first paragraph, for the alleged reason that the specification fails to provide a written description of a method of using a cytotoxic or imaging agent alone and not conjugated to a protein or antibody with the method of administering D-lysine or poly-lysine. Applicants respectfully traverse this rejection.

The Examiner has interpreted claim 38 as requiring that a cytotoxic or imaging agent be administered alone. However, the claim does not state this. The claim is simply silent with regard to the protein conjugate, it does not exclude it. The specification provides a written description for the administration of cytotoxic and imaging agents to a subject. The specification describes in detail how cytotoxic agents and imaging agents are administered and how these same agents may contribute to renal nephrotoxicity or interfere with accurate radioimaging.. Thus, contrary to the Examiner's assertion, it is not new matter to present a claim that recites an improvement of a therapeutic or diagnostic method comprising administering a cytotoxic agent or an imaging isotope. However, applicants wish to advance the allowance of this claim. Accordingly, applicants have amended claim 38 to recite "a protein conjugate comprising a cytotoxic agent or an imaging isotope." In view of this amendment, applicants respectfully request the Examiner to withdraw this rejection.

In paragraph 11, the Examiner rejects claims 19 and 38 under 35 USC § 112, first paragraph, for the alleged reason that the specification fails to enable a method of using a cytotoxic or imaging agent or just any metabolic product or peptide, polypeptides, glycoproteins,

lipoproteins, antibodies or antibody fragments and administering D-lysine or poly-lysine having a molecular weight of 1-60 kD.. Applicants respectfully traverse this rejection and interpret this rejection to be based upon the Examiner's assumption that applicants intend to claim a method using "unconjugated" proteins, etc. As indicated above, applicants have amended claim 38 to recite protein conjugates.

With regard to claim 19, applicants direct the Examiner's attention to page 12, first paragraph, of the specification wherein applicants state that "[m]etabolic products of the above cytotoxic agent conjugates and the radiolabeled conjugates are also included within the scope of the present invention." This recognizes the fact that in the body, the proteins, antibodies, antibody fragments, glycoproteins and lipoproteins can be altered or metabolized in the normal course of therapy or diagnosis. However, applicants also believe that such metabolic products are peptide conjugates. For instance, antibody fragment conjugates that have undergone degradation are peptide conjugates. Accordingly, applicants herewith delete the term "metabolic products thereof" with the understanding that this embodiment is encompassed by the term "peptide conjugate," which remains in the claim. Withdrawal of the rejection in paragraph 11 is therefore respectfully requested.

In paragraph 12, the Examiner rejects claims 19, 38 and 40 under 35 USC § 112, second paragraph, as being indefinite. Claim 19 is alleged to be indefinite for reciting "metabolic products thereof." With regard to claim 38, the Examiner alleges there is no antecedent basis for "imaging agent." Claim 40 is alleged to be indefinite for reciting ONCONASE and the examiner asks applicants to amend the specification to recite the common generic form of this trademark.

In response, applicants point out that with the entry of the above amendment, claim 19 no longer recites "metabolic products thereof;" claim 38 now recites imaging isotope, for which there is an antecedent; and, the term ONCONASE in claim 40 is amended, as is the specification to add at page 8, first full paragraph, "ranpirnase", which is a generic description. Applicants also add ® in the claim and in paragraph 8. Thus, applicants respectfully request the Examiner to withdraw the rejections set forth in paragraph 12.

## **V. REJECTIONS UNDER 35 USC § 102**

In paragraph 13, the Examiner rejects claims 1-8, 11-19, 23-28, 31-39 and 41 under 35 USC §102 (b) over Behr *et al*, *Cancer Research* 55: 3825-3834 (1995) ("Behr - 1995").

According to the Examiner, this rejection is proper in view of the claims' failure to be granted benefit of priority of the '899 application. Applicants respectfully traverse this rejection for reasons set forth above in connection with the priority issue. That is, all of the independent claims should be granted the benefit of the parent case's filing date, March 21, 1995. As such, Behr-1995 is not prior art and this rejection should be withdrawn. Applicants respectfully request favorable reconsideration of the priority issue.

With regard to new claims 42 and 43, applicants assert that Behr- 1995 nowhere discloses a method of increasing by at least 2- fold or 2-3 -fold the pharmaceutically acceptable dosage of a protein conjugate for therapeutic or diagnostic purposes. Thus, the rejection based on Behr-95 is not applicable to claims 42 and 43. Allowance thereof is respectfully requested.

## **VI. REJECTIONS UNDER 35 USC § 103**

In paragraph 14, the Examiner rejects claims 1-9, 11-21, 23-29 and 31-41 under 35 USC § 103 (a) as being unpatentable over Behr *et al*, *Cancer Research* 55: 3825-3834 (1995) ("Behr-1995") and in view of Grey *et al*., U.S. Patent No. 5,380,513 ("Grey") and Raines, U.S. Patent No 5,840,296 ("Raines").

According to the Examiner, Behr teaches a method of reducing renal uptake of a protein conjugate of an antibody fragment of Fab' of which when conjugated is less than 60kD comprising an imaging or therapeutic moiety in a patient (mouse model) with the addition of D-lysine and poly-lysine (15-30kD) and further teaches that the solutions were administered by iv or ip or orally and two compounds were administered together. The Examiner admits that Behr does not teach a protein conjugate comprising a ribonuclease or ONCONASE but cites Grey and Raines to compensate for such deficiency. That is, the Examiner states that Grey teaches a method of reducing renal retention of protein conjugates with lysine, the conjugates comprising imaging agents and therapeutic agents that comprise cytotoxins and the proteins comprise receptors and enzymes as well as other proteins. Grey also is said to teach administration orally, by iv, ip or the like. The Examiner characterizes Raines as teaching conjugates comprising ribonuclease which conjugates comprising ribonuclease which have been effective in tumor patients and the decrease in renal function of ONCONASE may be the consequence or an inability to effectively clear the ONCONASE protein from kidneys. ONCONASE is said to be a 104 amino acid protein which is not greater than 60kD.

The Examiner concludes that one of ordinary skill in the art would have been motivated to and had a reasonable expectation success to have produced a method for reducing kidney retention of protein conjugates in a patient with administration of compounds of lysine or poly-lysine in view of Behr -1995, Grey and Raines. Applicants respectfully traverse this rejection.

First, applicants again urge the Examiner to grant the present claims the benefit of the March 31, 1995 filing date, for the reasons set forth above. In the absence of Behr-1995, the Examiner's rejection is insupportable. Grey teaches the art over which applicants' invention is an improvement. It no where teaches or suggests the claimed method administering to said patient one or more compounds selected from the group consisting of D-lysine, poly-lysine having a molecular weight in the range 1-60 kD, pharmaceutically acceptable salts thereof and carboxyl derivatives thereof, wherein said protein conjugate has a molecular weight that is not greater than about 60 kD. Raines' disclosure of conjugates comprising ribonuclease and Onconase does not cure the deficiencies in Grey. Applicants again urge the Examiner to afford this application the benefit of the parent's filing date and to accordingly withdraw this rejection under 35 USC § 103.

## **VII. DOUBLE PATENTING REJECTION**

The Examiner provisionally rejects claims 1-9, 11-21, 23-29 and 31-41 under the judicially created doctrine of obviousness-type double patenting over claims 38-47 of copending application No. 10/438,219. The examiner states that claims in the instant application encompass and anticipate the claims in the '219 application. Both claim sets are directed to a method of reducing kidney retention of a protein conjugate or agent by administering D-lysine or poly-lysine in the range of 1-60 kD. Because applicants have not received a notification of allowable subject matter for either case, applicants request this rejection be set aside until such indication is forthcoming.

**CONCLUSION**

In view of the above amendment and arguments, applicants respectfully request Examiner Helms to reconsider and grant the amended claims the benefit of the earliest priority date. Applicants also respectfully request Examiner Helms to withdraw all prior art rejections. In view of the amendment, applicants urge that all rejections under 35 USC § 112 have been addressed and overcome. Withdrawal of all § 112 rejections is therefore respectfully requested. Applicants assert that the provisional double patenting rejection will be addressed when they receive an indication of allowable subject matter in both cases. A Notice of Allowance is therefore eagerly awaited.

Please direct all correspondence to the undersigned attorney at the address indicated below.

Respectfully submitted,

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